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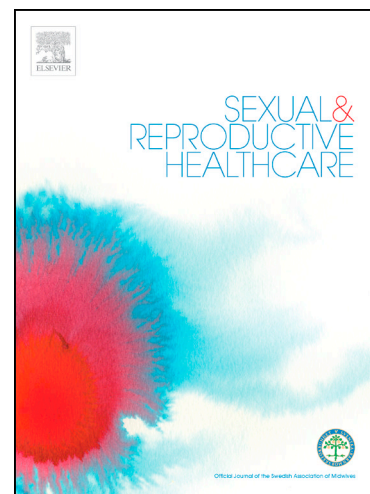
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## Accepted Manuscript

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# **Breastfeeding and skin-to-skin contact as non-pharmacological prevention of neonatal hypoglycemia in infants born to women with gestational diabetes; a Danish quasi-experimental study**

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## **Highlights:**

- Infants born to women with GDM are at increased risk of hypoglycemia in the early post-partum period
- A caring plan of frequent breastfeeding and skin-to-skin contact was successfully tested in a real-life setting
- The blood glucose values measured were well within the safety limits for the majority of infants
- The number of breastfeeds in the first six hours post-partum almost doubled and exclusive breastfeeding was obtained
- Only 1 in 5 infants required formula supplementation, compared to 5 in 5 infants in the control group

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# **Skin-to-skin contact and frequent breastfeeding as non-pharmacological prevention of neonatal hypoglycemia in infants born to women with gestational diabetes; a Danish quasi-experimental study**

## **Abstract**

**Objective:** To investigate the effect on infant blood glucose levels of an intervention consisting of early, frequent breastfeeding and two hours of immediate uninterrupted skin-to-skin contact following birth of term infants born to mothers with diet-treated gestational diabetes (GDM).

**Study design:** Quasi-experimental study design with a historical control group (n=132) and an intervention group (n=401) testing a procedure to prevent neonatal hypoglycemia.

**Main outcome measures:** Data collection on blood glucose levels, hypoglycemia incidence with a cut-off of  $< 2.5$  mmol/l, breastfeeding within the first two hours after birth, frequency within the first six hours, and amount of formula given to hypoglycemic infants.

**Results:** Mean blood glucose levels in the intervention group at two and four hours were within safe limits: 3.37 mmol/l (95% CI: [3.30, 3.44]) and 3.40 mmol/l (95% CI: [3.34, 3.46]), respectively. Infants suffering a hypoglycemic event within four hours after birth decreased from 22.7 % (n=30/132) in the control group to 10.2 % (n=41/401) in the intervention group. The mean number of breastfeeds in the intervention group (six hours) was 2.41 compared to 1.34 in the control group (seven hours), an increase of 80%. Only 41 of 401 infants in the intervention group were interrupted in immediate interaction with their mother because of hypoglycemia. We failed to obtain sufficient data on skin-to-skin contact.

**Conclusion:** Maintaining skin-to-skin contact for infants of mothers with diet-treated GDM, monitoring blood glucose levels until obtaining two values  $> 2.4$  mmol/l and encouraging early frequent breastfeeding is a safe strategy to prevent hypoglycemia.

**Keywords;** neonatal hypoglycemia; frequent breastfeeding; gestational diabetes; skin-to-skin; SSC; infant

## **Introduction**

Worldwide, the incidence of maternal gestational diabetes mellitus (GDM) is increasing, and in the USA, it is as high as 10% [1,2]. In Denmark, approximately 2.3% of women develop GDM during pregnancy. Most often, GDM is associated with overweight and treated through dietary and lifestyle changes [3,4]. In addition to the well-known benefits of breastfeeding, mothers with GDM experience further benefits such as a more stable blood glucose level, reduced insulin resistance, and delay in developing type 2 diabetes [5]. For the infant, exclusive breastfeeding increases the likelihood of a stable body mass index (BMI) curve up to the age of five months, possibly preventing later obesity and/or type 2 diabetes [6,7]. Even though the Danish Health Authority recommends exclusive breastfeeding of the infant during the first six months, recent Danish data showed that only 18% of five-month old infants of mothers with GDM were exclusively breastfed compared to 41% of infants in a cohort of 18,687 infants born in 2014 [6,8].

Every infant born at term must adapt quickly to extra-uterine life with a metabolic response to intermittent feeding. Infants of mothers with diet-treated GDM (GDM mothers) may have an increased risk of failure in the metabolic response resulting in episodes of hypoglycemia [9]. In the post-natal transition from using placental glucose, fat is released by ketogenesis from adipose tissue stores, glycogenesis is initiated, and sources from ingested breastmilk are a part of the process to ensure a proper metabolic response in the infant [10]. The former practice in Denmark concerning prevention of neonatal hypoglycemia in infants at risk has been ingestion of weight-adjusted formula (60 ml/kg/day the first 12-24 hours starting one hour post-partum and repeated every two-three hours) [11]. However, all infants seem to have a physiological fall in blood glucose within the first one to three hours post-partum regardless of feeding [12,13]. In a population of infants not at risk, 9.1% had a blood glucose level below 2.2 mmol/l within the first two hours of life [14]. The early post-natal period is important to establish breastfeeding, and former practice has challenged establishment of initial breastfeeding as the infant was separated from the mother for blood samples and formula supplementation.

Colostrum contains all the nutrients needed in the transition from womb to extrauterine life [15,16]. Early intake of colostrum activates brain protection resources more than formula [17], enhancing activation of the infant immune system [18,19]. Formula supplementation during the first hours may make the infant inactive and reduce sucking at the breast, which may delay ingestion of colostrum as well as complicate establishment of breastfeeding and lactation. This can cause a perceived delay in breast milk coming-in and thus reduced milk supply with risk of cessation in first-time mothers [6,19,20]. The Academy of Breastfeeding Medicine states that 1 to 3 ml of colostrum or formula every two hours is the recommended practice if a hypoglycemic event occurs [16]. Skin-to-skin contact (SSC) right after birth has proven to be temperature stabilizing, glucose sparing, and to decrease the release of stress hormones that increase glucose utilization [21]. Besides, it enhances mother-infant bonding. Furthermore, unlimited SSC enhances episodes

of instinctive behavior, alertness and suckling [21]. However, none of the available studies include infants of GDM mothers.

Knowledge is sparse on breastfeeding as a non-pharmacological treatment in infants of mothers with GDM. In a pilot study from 2009, Chertok et al. found fewer events of hypoglycemia among breastfed infants (9%) compared to formula-fed infants (46%) within the first three hours of life [22]. In studies regarding neonatal hypoglycemia, data is often sparse on breastfeeding frequency. Flores-le Roux et al. included 190 breastfed infants of mothers with GDM, but without data on breastfeeding frequency [23]. Thus, there is a gap in knowledge on whether breastfeeding combined with SSC is a safe way to prevent hypoglycemia in healthy infants born at term of GDM mothers.

The aim of the study was to test whether SSC and early, frequent breastfeeding will help to establish blood glucose levels above 2.4 mmol/l during the first four hours post-partum compared to routine early feeding with weight-adjusted intake of formula in infants of mothers with GDM. Furthermore, to investigate if SSC increased breastfeeding frequency in the first hours after birth.

## **Methods**

### **Design**

A quasi-experimental study design with a historical control group was used to investigate the effect on blood glucose levels of an intervention with frequent breastfeeding and at least two hours of uninterrupted SSC in healthy infants of GDM mothers.

### **Setting and former practice**

The intervention took place at Aalborg University Hospital in Denmark where 2.4-4.1% of new mothers are diagnosed with diet-treated GDM. The standard procedure before 1 May 2009 was to weigh the infant, give K vitamin and obtain bedside blood glucose values from blood sampled from the infant's heel within the first hour post-partum. SSC was practiced with variations, as there was no policy regarding SSC within the first hour post-partum before 1.10.2010. Regardless of breastfeeding or not, formula supplementation was given followed by new blood glucose sampling at two, four, six, and 12 hours post-partum. The infant received a weight-adjusted amount of formula (60 ml/kg/day) regardless of the blood glucose level, and breastfeeding was attempted at four, seven, and 11 hours post-partum. If the blood glucose level at any time was below 1.7 mmol/l, a pediatrician was immediately consulted.

### **Content and intervention**

A change in the routine formula supplementation for infants of GDM mothers was debated during an interdisciplinary meeting between obstetricians, pediatricians, leading midwives, and lactation consultants in January 2009. Following this debate, the first author (BD) with the support of the chief pediatrician designed a new procedure consisting of two parts: A breastfeeding-support part and a blood glucose-measurement part. On 2 March 2009, all relevant health professionals were introduced to the new "Caring plan to prevent

and treat hypoglycemia in infants of mothers with diet-treated GDM” (Caring plan-GDM (Figure 1)) and data from the Caring plan-GDM was documented in a special form at the maternity ward. Meetings were held for leading midwives in April 2009 to ensure the implementation starting in the delivery room. The first author was available for questions and comments. After pilot testing in April, chart audits and feedback led to slight adjustments of the chart. Data collection in the intervention group started on 1 May 2009.

The intervention consisted of a pre-natal and a post-natal part. During pregnancy, GDM mothers received written information concerning the post-partum period explaining why and how early SSC, frequent breastfeeding, and hand expression of colostrum could benefit both mother and infant. To promote SSC, defined as placing the naked infant in prone position between the mother’s breasts [24], the midwives postponed anthropometric measurements until two hours after birth. The mothers were encouraged to maintain SSC with their infant for at least two hours and were assisted verbally and practically to initiate breastfeeding. If an infant, after trying itself or with assistance, did not suckle successfully within the first two hours after birth, mother and infant were transferred from the delivery room to the maternity ward as usual, but the infant maintained SSC to stimulate suckling behavior [25]. The mother was instructed in hand expression of colostrum and how to give it to her infant, if the infant did not suckle effectively during the first two hours or three hours since the last feed, as an attempt to achieve at least eight feedings /24 hours [16]. Furthermore, mothers were encouraged by staff to practice SSC repeatedly or continuously for the following 12 hours or more and to stimulate frequent breastfeeding.

Observation of and action on the infant’s glycemic state was conducted two hours post-partum unless symptoms of hypoglycemia occurred before. From 1 May 2009, bedside blood glucose values of the infant were obtained at two and four hours post-partum and continued until two consecutive values were 2.5 mmol/l or above. The time points for sampling were selected considering the normal physiological drop in blood glucose level after birth. If the blood glucose level was below 2.5 mmol/l, the infant was supplemented with 3 ml per kg per feeding of breastmilk or formula [16]. Low blood glucose levels at two consecutive time points increased the amount of supplementation every third hour to 6 ml per kg per feeding. If the blood glucose level fell to or below 1.7 mmol/l, a pediatrician was consulted.

### *Figure 1*

Caring plan to prevent and treat hypoglycemia for infants of mothers with diet-treated GDM

Abbreviations; SSC= skin-to-skin contact. pp= post-partum. dyad= mother and infant. BM= expressed breast milk. F = formula. Lact-aid= feeding tube and syringe inserted in the mouth, while the infant is suckling.

The more at the right in the chart, the more severe signs of hypoglycemia is apparent, and the colors of the boxes start as white as a natural pathway with no need of supplementation. A darker color indicates lower glucose values, higher amount of supplementation and signals action. The darkest color demands the need of a pediatrician. Red line under a box indicates no need for further tests are required.



### Study population

The study population consisted of a prospective intervention group (IG) and a retrospective historical control group (CG) of GDM mothers. Women in the IG and CG gave birth in the periods 1 May 2009 until 31 December 2013, and 1 October 2006 until 28 February 2009, respectively. The starting point for data collection in the CG was limited to October 2006 because of a change in bedside blood sampling, instruments, and implementation of a new laboratory program in September 2006.

For the whole study period, screening for gestational diabetes remained unchanged. During pregnancy, GDM was diagnosed if the blood glucose level was above 9.0 mmol/l two hours after a 75-g oral glucose tolerance test, and the pregnant woman was encouraged to start a dietary intervention and blood glucose profiling after meeting a dietician, an obstetrician and a nurse. Further details on the GDM protocol are described by Fenger-Grøn et al. [6]. All mothers diagnosed with GDM and treated by diet were admitted to the maternity ward for at least 12 hours post-partum.

Inclusion criteria for both groups were diet-treated GDM in mothers and gestational age > 36 weeks, birthweight > 2500 g, Apgar score > 8/5, umbilical cord, vein/artery PH > 7.0, and admitted to the maternity ward. Exclusion criteria for infants in both groups were severe clinical and anthropometric dysmaturity demanding specialized care.

In the intervention period, there were 15,283 births whereof 632 mothers (4.1%) had GDM and 401 infants and their mothers met the inclusion criteria. In the control period, there were 8,411 births whereof 200 women had GDM (2.4%) and 137 infants and their mothers met the inclusion criteria (Figure 2).

### *Figure 2*

Flowchart. Number of infants born to mothers with diet-treated GDM in the study period.

For each group, the reasons for and the total number of infants excluded are stated.

### Measurements and data collection

Measurements of blood glucose were recorded at two and four hours for both groups and obtained by a heel prick test taking aseptic precautions with POCT chromogen reagent strips and ACCU-CHEK Inform II Blood Glucose Monitoring System, validated for infants, from Roche Boehringer Mannheim Diagnostics Systems, Inc, Sommerville, New Jersey. A hypoglycemic event was defined as blood sugar level equal to or lower than 2.4 mmol/l [26,27]. Data was registered in a laboratory database (LABKA).



Three different feeding modalities were registered: breastfeeding, formula, and expressed colostrum. A breastfeeding episode was characterized by the infant suckling continuously for several minutes without getting off the breast and by a swallowing sound, based on elements from LATCH score [28]. Formula includes any amount of formula feeding. Expressed colostrum refers to the mother's own hand-expressed colostrum. The number of breastfeedings was registered up to six hours post-partum for the IG, where infants had unlimited recorded breast access and up to seven hours postpartum for the CG, where infants were encouraged to breastfeed at four and seven hours. After six hours, breastfeeding was not recorded as detailed in the IG. Likewise, the amount (ml) of formula supplementation was registered up to six hours after birth in the IG and up to seven hours in the CG. Data on SSC in the first two hours was to be recorded on registration sheets after information from the mother.

Additional data collected on the infants included sex, gestational age (GA), and birth weight (BW). Data collected on the mothers included age, smoking status, BMI, parity, hypertension, thyroid disease, singleton or twin pregnancy, intention to breastfeed, and delivery mode. Data on breastfeeding behavior and supplementation for the IG was collected in registration sheets and monthly transcribed into datasheets with additional data collection and rechecked in the system for abnormalities and registered in a local database (Koorint). A corresponding registration sheet was made for the CG and each nurse chart in the period was searched for possible diet treated GDM mothers, re-checked, and registered.

Additional data for the IG and CG was abstracted and confirmed by the first and last author from local databases and electronic collaborating systems: A) nursing handwritten charts; data about feeding and amount given in every mother-infant dyad for the first six-seven hours post-partum. B) hospital birth registration database (AS-400); Birth and delivery data, infant demographic data, as well as maternal age, parity, BMI, HbA1C, smoking status. C) medical electronic recordings (Clinical Suite); Data on hypertension, thyroid disease. D) laboratory (LABKA) test results, HbA1C and updates on thyroid disease. The oldest HbA1C - values were converted from % to mmol/l. No data was collected on use of medication.

#### Ethics and approval

Study protocol and data collection were approved by the Region North Committee on Health Research Ethics and reported to the Danish Data Protection Agency, number 2008-58-0028/2013-27.

#### Statistics

Continuous variables are presented as mean and standard deviation or median and range depending on their distribution. Categorical variables are presented as frequencies and percentages. Comparisons between IG and CG were made using median or t-tests for continuous variables, depending on their distribution, and chi-squared tests for categorical variables. Multiple linear or logistic regression was used for the adjusted analyses of blood glucose levels and hypoglycemic events between groups. There was no imputation of

missing data for the adjusted analysis, only complete cases were used. In the tables, for each variable we reported the number of available observations in the IG and CG, respectively. Poisson regression was used to compare the breastfeeding frequency between the two groups. Statistical analyses were made in Stata 13. Results with p-values below 0.05 were considered statistically significant.

## **Results**

There were 394 mothers and 401 infants in the IG and 130 mothers and 132 infants in CG. Clinical and demographic characteristics of mothers and infants showed that the two groups are essentially comparable (Table 1). Regarding the mothers, we found no statistically significant differences in age, parity, smoking status, thyroid disease or delivery mode. The two groups showed statistically significant differences regarding BMI, hypertension, and HbA1C (all higher in the CG). For infants, we found no statistically significant differences in gestational age, birth weight, or sex distribution. In the IG, 4.2% of mothers chose not to breastfeed, while it was 2.3% in the CG; this difference was, however, not statistically significant.

*Table 1 here.*

Looking at all infants, blood glucose levels at two hours post-partum were comparable in the IG and CG (Table 2a). Four hours after birth, blood glucose was significantly higher in the IG than in the CG. Both in IG and CG at two and four hours the mean blood glucose level was well above the limit of 2.5 mmol/l (Table 2a). The proportion of infants with hypoglycemic events at two hours was 2.3 times higher in the CG than in the IG (Table 2b). At four hours, it was 3.8 times higher in the CG (Table 2b). The pattern was the same restricting the analysis to infants who successfully breastfed within the first two hours after birth. We found significantly higher blood glucose levels in the IG after four hours, and well above the 2.5 mmol/l limit in IG and CG (Table 2a), and significantly fewer hypoglycemic events in the IG (Table 2b). Adjusting the analysis for variables such as maternal age, smoking status, BMI, HbA1C, thyroid disease, hypertension, parity, delivery mode, birthweight, or gestational age did not influence the results (data not shown).

*Table 2a here*

*Table 2b here*

The different feeding modalities (breastfeeding, expressed colostrum, and formula feeding) in the IG and GC are shown in Table 3. All infants in the CG (132) received formula supplementation according to the protocol at the time. In the IG, only 73 (18.2%) of the infants received formula. Data on breastfeeding frequency – or lack of - was available for more than 90% of the infants in both groups: 374 infants in the intervention group and 122 infants in the control group. The percentage of infants not breastfed within the first two hours was significantly lower in the IG (6.6%) than in the CG (36.9%). Figure 3 shows the number of breastfeeding episodes per infant in each group, demonstrating a much higher frequency in the IG. The

mean breastfeeding frequency during the first six hours post-partum in the IG was 2.4 times (95% CI [2.2, 2.6]) compared to 1.3 times (95% CI [1.1, 1.5]) within the first seven hours in the CG, equivalent to an increase of 80% (Poisson P-value < 0.001).

*Table 3 here*

*Figure 3*

Boxplots of number of breastfeeds per infant in the first hours after birth in the IG (up to six hours) and CG (up to seven hours).

The hypoglycemic infants in the IG received much less formula than their peers in the CG (median 5.5 ml/kg vs. 19 ml/kg, data not shown); seven infants had 3ml/kg as recommended. Among the infants receiving formula in the IG, 39 were due to low blood glucose levels (at two or four hours). Our infants received supplement in this real life setting for various reasons other than hypoglycemic events. In other cases, the mother choose not to breastfeed (n17), the mother requesting formula supplementation (n13), a tired mother or in OR, a hungry infant or unable to latch, or polycythemia were reasons for infants receiving supplement. No infant was given expressed colostrum to correct hypoglycemic events; four infants were given expressed colostrum after four and six hours due to not suckling effectively or not at all.

The SSC data available generally only included information from the first hour of life. Since the mothers were not asked about SSC in the first two hours when arriving to the maternity ward, we cannot analyze the effect of SSC on blood glucose or breastfeeding frequency, or whether it was longer in the IG.

## **Discussion**

Previous studies on infants born to GDM mothers have been mostly descriptive and focused on hypoglycemic events and have contributed with little information about breastfeeding. This study showed safe blood glucose levels, a significant decrease in episodes of hypoglycemia, and a significant increase in the frequency of breastfeeding using a non-pharmacological intervention consisting of SSC and support and encouragement to frequent breastfeeding in the early post-partum period in infants of GDM mothers. The number of infants receiving formula was reduced from 100% in the CG to 18.2 % in the IG. To our knowledge, this is the largest study on infants born to GDM mothers with specific data on blood glucose levels, breastfeeding within the first two hours and the first six hours post-partum.

With a blood glucose level at two and four hours that was comparable or higher in the IG than in CG it seemed that early frequent breastfeeding and infant SSC is a safe strategy to prevent hypoglycemia in infants. Our early results on blood glucose level (3.36 mmol/l,) were slightly higher than the ones found in

the pilot study by Chertok et al. (3.20 mmol/l) for breastfed infants at 1.9 hours [22]. Their inclusion of 11% insulin-treated mothers may explain the difference, or the adding of infant SSC practices in the present Caring plan-GDM may have contributed to the slightly higher blood glucose level. The HAPO study found glucose levels in non GDM-affected infants (3.3 mmol/l) comparable to our findings at 3-5 hours post-partum but these results were without supplemental data on SSC or breastfeeding frequency [14,22]. The blood glucose levels observed were similar when investigating all infants and when focusing only on those breastfed within two hours post-partum. This seems to support the AAP that states blood glucose level in the first hours are independent of feeding status [13], although low numbers of exclusively formula-fed infants in our study prevented a direct comparison. Undisturbed and frequent breastfeeding in the first six hours might help to establish breastfeeding [21]. In the Caring plan-GDM, we chose to measure blood glucose at two and four hours post-partum and to intervene at a blood glucose level  $< 2.5$  mmol/l. Recently, the study of Tozier et al. integrated the physiological fall in the blood glucose level in their algorithm and allowed the infant under observation (in all diabetes groups,  $n=77$ ) to reach a blood glucose level  $>2.2$  mmol/l at four hours [29]. This study suggested, similar to ours, to keep the infant SSC and breastfeed or give drops of colostrum if the infant was not suckling and to only intervene if the blood glucose level fell below 1.3 mmol/l or symptoms of hypoglycemia occurred [29].

In the present study, the incidence of hypoglycemia defined as blood glucose levels  $< 2.5$  mmol/l was 7.1% at two hours and 3.8% at four hours in the IG. The study by Flores-le Roux et al. reported 20% of infants of diet-treated GDM mothers to have hypoglycemic events [23]. The difference in incidence of hypoglycemia may be explained by the intervention of SSC and breastfeeding behavior in the Caring plan-GDM. No specific data on breastfeeding was, however, reported in the study by Flores-le Roux [23]. Our data showed that 7% of breastfed SSC infants had hypoglycemic events at two hours. HAPO ( $n=17,000$ ) showed that 9.1% of infants not affected by GDM had blood glucose levels below 2.2 mmol/l [14]. In our IG, 16 (4%) had a blood glucose level below 2.2 mmol/l at two or four hours indicating that our Caring plan-GDM may contribute to prevent hypoglycemia, showing morbidity levels comparable to infants born at term regarding hypoglycemic events [1]. Moreover, in the study of Chertok et al. as well as in the HAPO study, the breastfed infants who were rooming-in had a lower incidence of hypoglycemia compared to the non-breastfed/formula-fed infants, suggesting that keeping mother and infant together, breastfeeding has a preventive effect on hypoglycemia [14,22]; after investigating the possible influence of previous birth, we could not find a significant association.

With only 6.6% of infants not suckling within the first two hours post-partum in the IG compared to 36.9% in CG, it seemed that our Caring plan-GDM gave mothers and infants in the IG more opportunities to establish breastfeeding, also shown by a steep increase in breastfeeding frequency within the first six hours

compared to the CG. According to Essa et. al, 88% of SSC infants achieved a successful first breastfeeding compared to 42% of non-SSC infants [24], supporting our findings on breastfeeding initiation within the first two hours. Csont et al. also found a significant increase in the number of breastfeedings, among the 65 infants post intervention, in the four hours it took to achieve three blood glucose measurements above 2.5 mmol/l [9]. In their study, only 24.6% of the mothers were affected by diabetes [9]. In our study, the mean amount of formula given to hypoglycemic infants in the IG was 5.5 ml/kg. Seven hypoglycemic infants in the IG were given 3 ml/kg of formula as recommended in the Caring plan-GDM, and we failed at giving expressed colostrum to these infants, since they were all exclusively supplemented with formula. Only two infants in the IG received formula twice. One infant > 4500 grams (4820 grams) received 65 ml two hours post-partum as a response to a blood glucose level of 1.7 mmol/l. Despite this, we reduced the volume by approximately 40 ml per hypoglycemic infant for the first six hours; from 19 ml/kg/seven hours to 5.5 ml/kg/six hours. Tozier et al. in their study reduced the number of infants supplemented by formula with 53.6% [29]. Changing strategies in a complex hospital environment can make staff react in different ways. The study by Csont et al. reported that half of the staff were uncomfortable giving only small amounts of colostrum or formula as they did not believe it would be preventive [9]. This could also be the case in our study, as staff showed low compliance for colostrum use in the early hours post-partum in the delivery room and in the maternity ward. ABM's revision of prevention of neonatal hypoglycemia from 2014 recommends to give 1-3 ml/ kg supplementation every two hours, increasing the difference between the suggested and our actual amount [16]. Small amounts of supplementation could signal to the mother that her ability to breastfeed her infant is adequate and that small amounts of hand expressed colostrum are sufficient to satisfy the needs of the vulnerable infant, as well as to increase the infant's interest in suckling [9,16,30]. Thus, early breastfeeding should be enhanced. Having a time limit for trial and error before changing feeding strategy and start of hand expression could promote breastfeeding further and keep safety goals together with using small amounts of colostrum or formula if needed [9].

Our study population included only healthy infants born at term to GDM mothers admitted to a maternity ward. A strength of the study was the prospective inclusion of participants, and the possibility of having a retrospective control group based on the same GDM criteria. In our Caring plan-GDM, SSC was an important part of the planned intervention. Although the Caring plan-GDM states SSC for at least the first two hours after birth, this was in some cases not possible. The lack of data on SSC for each infant unfortunately prevented us from analyzing the effect of this important component of the Caring plan-GDM. Likewise, we were unable to make separate analyses for breastfed and non-breastfed infants as was intended. Most of the infants in our CG have presumably not been maintained SSC but were supplemented with formula within the first hour post-partum. In the IG period, implementation of continuous SSC right after birth and for the first hour was ongoing, as a quality indicator in Denmark from October 1, 2010. SSC is well

known to stabilize the infant and increase infant alertness [21,24], and our results on blood glucose and breastfeeding frequency could partly be a consequence of SSC, but must remain unproven for our group of infants.

Blood glucose samples were not tested in the laboratory to confirm low levels, but throughout the entire period we used the same validated sampling method. Even though the IG data was collected for six hours compared to seven hours in the CG, the mothers in the IG still breastfed significantly more times. A weakness of comparing the IG to a historical CG lies in the potential demographic differences between the groups, but the effect of such differences was investigated and appeared to be insignificant. Demographic characteristics of mothers were comparable between the two groups, except for BMI, HbA1C and hypertension in pregnancy ( $p = 0.002$ ). Hypertension did not affect our results, but the analysis should be interpreted with caution because of the small study sample (CG 24/132, IG 33/401). There were less women with a BMI above 30 in our IG and a BMI above 30 is known to increase the risk of neonatal hypoglycemia; we could not confirm this in our analysis [31]. In our study, 4.1% of pregnant women were diagnosed with GDM and treated by diet in the IG in the largest hospital in North Denmark Region (589148 inhabitants in 2018). It was above the 2.4% in our CG and even higher than the national average of 2.3% in 2010 [3]. This difference may indicate a larger number of pregnant women with factors making GDM screening relevant as seen worldwide, which increases the number of women diagnosed with GDM. The difference in HbA1C cannot be explained besides a different distribution in BMI and maybe a better compliance with dietary treatment. We need to ensure best practice to support GDM mothers in succeeding in breastfeeding and change existing evidence of lower breastfeeding rates [19]. Our results should not be used in adapting the Caring plan-GDM to other groups of infants at risk of neonatal hypoglycemia.

### **Implications to practice**

We have shown that implementing our Caring plan-GDM enabled infants to achieve a normal blood glucose level and thereby prevent hypoglycemia. By monitoring glucose levels and practicing two hours of SSC without external interferences and frequent breastfeeding, we are aligned with the 2016 statement of Rozance et al. showing that breastfeeding is a powerful factor in preventing neonatal hypoglycemia together with SSC [30,32]. The implementation of this non-pharmacological Caring Plan-GDM encourages to supplement the hypoglycemic infant with hand expressed colostrum before turning to formula supplementation. This particular change in practice, which was not followed in the present study, may point to a need to identify the barriers among health professionals in clinical practice.

### **Conclusion**

Our study adds to the existing evidence on SSC, combined with frequent breastfeeding, to prevent hypoglycemia, testing this on a population of healthy infants of GDM mothers. Monitoring infant glucose levels with SSC and free access to the breast proved a safe and blood glucose stabilizing strategy in the first



hours post-partum. This is just as, or maybe even more, effective than the former strategy in the CG. Breastfeeding frequency almost doubled compared to our controls. Expressed colostrum was not used to replace formula as suggested in the Caring plan-GDM and further research in the use of expressed colostrum could help ensuring a post-partum period, as normal as for infants not affected by GDM.

SSC in the early post-partum hours in these infants at risk might have supported and encouraged more frequent breastfeeding and thereby exclusive early breastfeeding. The effect of SSC during the first hours should be investigated further in infants of GDM mothers to support the existing evidence on the effect on blood glucose levels and duration of breastfeeding. Caring plan-GDM might have the potential to be applied in the care of other infants at risk of suffering from neonatal hypoglycemia.

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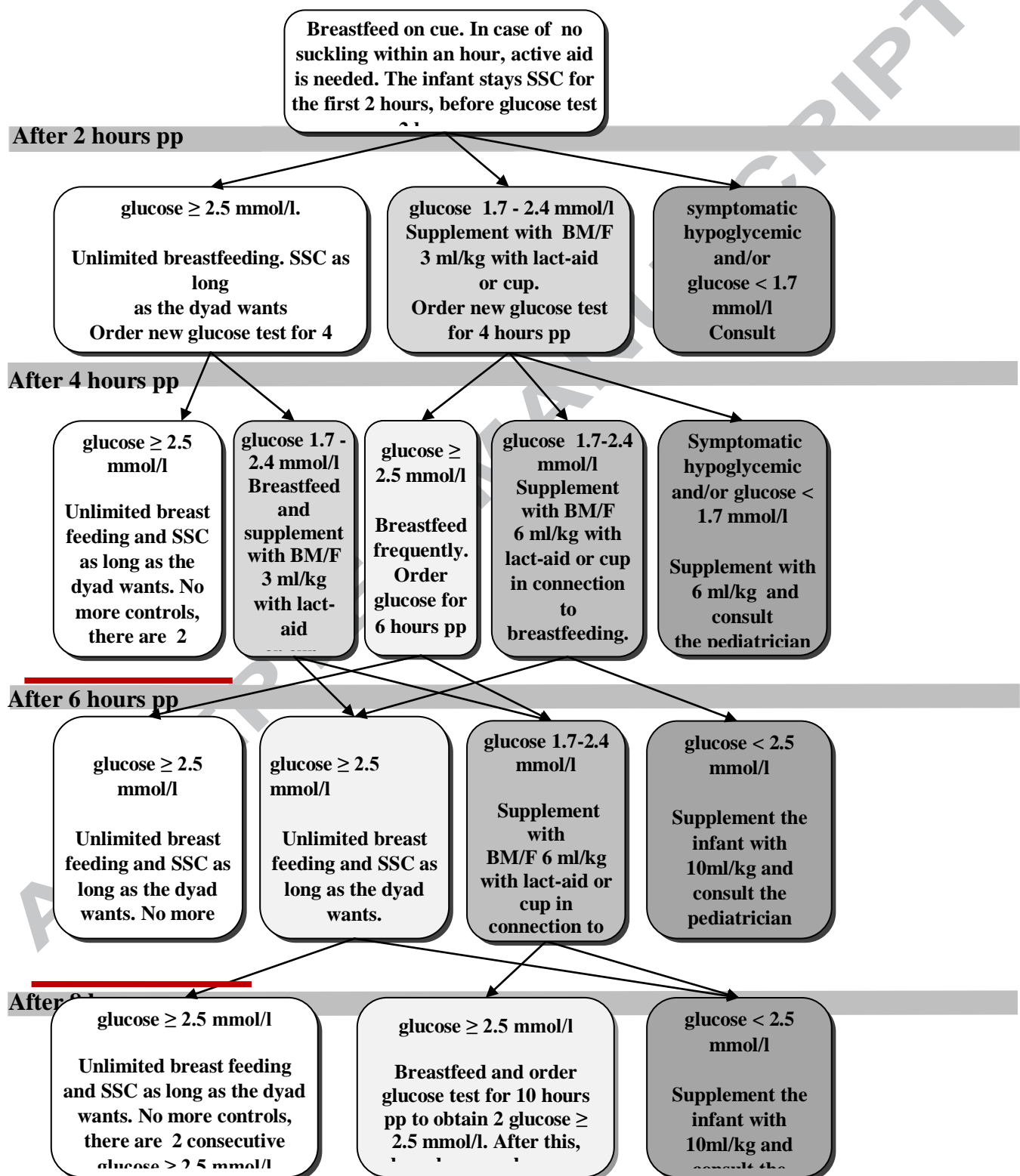
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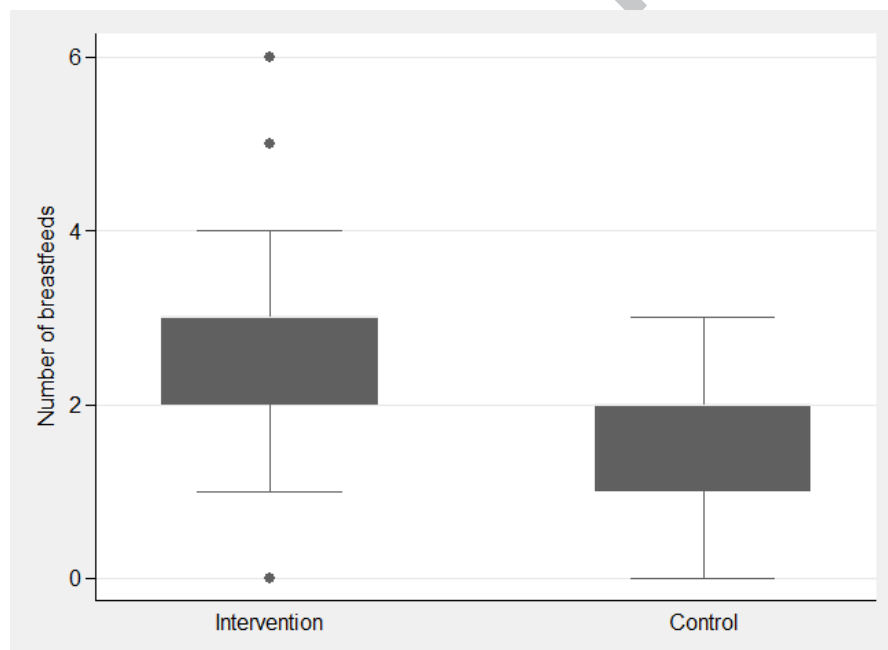
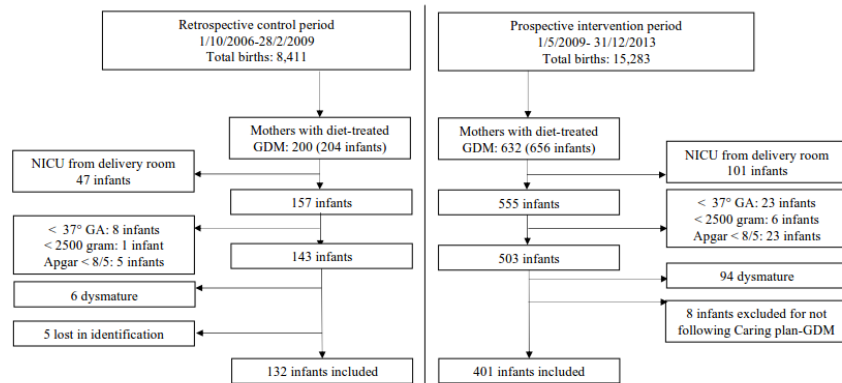


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# Tables

**Table 1**

Demographic characteristics of mothers and infants in the study.

	Intervention		Control		p
	n <sup>a</sup>	Statistic	n <sup>a</sup>	Statistic	
Mothers					
Age, years <sup>*</sup>	394	31.5 (5.2)	130	31.8 (4.6)	0.641
HbA1c mmol/l <sup>*</sup>	377	36.1 (5.0)	109	37.3 (4.0)	0.025
HbA1c ≥ 37mmol/l <sup>#</sup>	377	169 (44.8%)	109	63 (57.8%)	0.017
Singleton pregnancy <sup>#</sup>	394	387 (98.2%)	130	128 (98.5%)	0.856
Parity: multipara <sup>#</sup>	393	235 (59.8%)	130	78 (60.0%)	0.967
Smoker <sup>#</sup>	394	50 (12.7%)	130	21 (16.2%)	0.317
Hypertension <sup>#</sup>	391	33 (8.4%)	127	23 (18.1%)	0.002
Thyroid disease <sup>#</sup>	390	9 (2.3%)	128	7 (5.5%)	0.073
Cesarean birth <sup>#</sup>	394	92 (23.4%)	130	31 (23.8%)	0.908
BMI <sup>*</sup>	394	29.52 (0.32)	130	31.05 (0.55)	0.018
BMI <sup>#</sup>	394		130		0.076
< 25		109 (27.7%)		23 (17.7%)	
25 - 29.99		114 (28.9%)		36 (27.7%)	
30 - 34.99		100 (25.4%)		39 (30.0%)	
≥ 35		71 (18.0%)		32 (24.6%)	
Infants					
Sex: male <sup>#</sup>	401	206 (51.4%)	132	61 (46.2%)	0.304
Gestational age, weeks <sup>#</sup>	401		132		0.612
37 – 37.9		37 (9.2%)		9 (6.8%)	
38 – 38.9		83 (20.7%)		33 (25.0%)	
39 – 40.9		208 (51.9%)		69 (52.3%)	
≥ 41		73 (18.2%)		21 (15.9%)	
Birth weight, grams <sup>#</sup>	401		132		0.654
2500 – 2749		6 (1.5%)		3 (2.3%)	
2750 – 3999		297 (74.1%)		93 (70.5%)	
≥ 4000		98 (24.4%)		36 (27.3%)	

<sup>a</sup> number of mothers/infants with available information.

<sup>\*</sup> mean (sd); P-value from a t-test.

<sup>‡</sup> median [range]; only relevant for multipara women; P-value from a median test.

<sup>#</sup> number (percentage); P-value from a chi-squared test.

**Table 2a**

In separate file.

**Table 2b**

Number and percentage of infants with hypoglycemia two and four hours after birth in the IG and CG for all infants and only for infants breastfed within the first 2 hours after birth.

	All infants <sup>+</sup>			Infants breastfed within 2 hours <sup>+</sup>		
	Intervention n (%) <sup>#</sup>	Control n (%) <sup>#</sup>	p <sup>*</sup>	Intervention n (%) <sup>#</sup>	Control n (%) <sup>#</sup>	p <sup>*</sup>
<b>Hypoglycemia</b>						
<b>At 2 hours</b>	28 (7.1%)	21 (16.3%)	0.002	26 (7.0%)	14 (17.5%)	0.003
<b>At 4 hours</b>	15 (3.8%)	18 (14.5%)	<0.001	15 (4.1%)	12 (15.8%)	<0.001
<b>At 2 &amp; 4 hours</b>	2 (0.5%)	9 (6.8%)	<0.001	2 (0.5%)	6 (7.3%)	<0.001

<sup>#</sup> Number of infants with confirmed hypoglycemia and percentage from the total of children with available data at the given timepoint.

<sup>\*</sup> Chi-squared test.

**Table 3**

Feeding modalities 6 hours (IG) or 7 hours (CG) after birth.

	Intervention		Control	
	n	%	n	% <sup>a</sup>
<i>Breastfeeding, exclusive</i>	324	80.8	0	0
<i>Breastfeeding, in combination</i>	380	94.8	97	79.5 <sup>*</sup>
<i>Hand-expressed colostrum<sup>b</sup></i>	4	1	0	0
<i>Formula, exclusive</i>	17	4.2	25	20.5 <sup>*</sup>
<i>Formula, in combination</i>	73	18.2	132	100

<sup>a</sup> computed based on the number for which information is available. We use the total number in the group unless otherwise stated.

<sup>b</sup> these children did not receive formula.

<sup>\*</sup> data available for 122 children.



**Table 2a**

Blood sugar levels 2 and 4 hours after birth in the IG and CG for all infants and only for infants breastfed within the first 2 hours after birth.

	All infants					Infants breastfed within 2 hours				
	n <sup>#</sup>	Mean [95% CI]	n <sup>#</sup>	Mean [95% CI]	p <sup>*</sup>	n <sup>#</sup>	Mean [95% CI]	n <sup>#</sup>	Mean [95% CI]	p <sup>*</sup>
<b>Blood sugar</b>										
<b>2hours</b>	396	3.37 [3.30, 3.44]	129	3.27 [3.15, 3.40]	0.197	369	3.36 [3.28, 3.43]	80	3.22 [3.06, 3.37]	0.112
<b>4hours</b>	393	3.40 [3.34, 3.46]	124	3.20 [3.09, 3.31]	0.001	367	3.40 [3.34, 3.46]	76	3.17 [3.04, 3.31]	0.003

<sup>#</sup> Number of infants with data available.

<sup>\*</sup> Two-sample t-test.

Highlights:

- Infants born to women with GDM are at increased risk of hypoglycemia in the early post-partum period
- A caring plan of frequent breastfeeding and skin-to-skin contact was successfully tested in a real-life setting
- The blood glucose values measured were well within the safety limits for the majority of infants
- The number of breastfeeds in the first six hours post-partum almost doubled and exclusive breastfeeding was obtained
- Only 1 in 5 infants required formula supplementation, compared to 5 in 5 infants in the control group.